Study to Assess the Pharmacokinetic Drug - Drug Interactions between Atazanavir Plus Ritonavir Coadministered with Voriconazole in Healthy Subjects.

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Primary Objectives:• To assess the effects of VOR 200 mg BID on the steady-state PK of ATV administered as ATV/RTV300/100 mg QD in healthy subjects• To assess the effects of ATV/RTV 300/100 mg QD on the steady-state PK of VOR 200 mg BID inhealthy...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON32959

Source
ToetsingOnline

Brief title
ROMA

Condition

- Other condition
- Fungal infectious disorders

Synonym
HIV and Fungal infection

Health condition

HIV infectie

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: drug interaction, Fungal infection, HIV, Pharmacokinetic

Outcome measures

Primary outcome

• Pharmacokinetic Measures: Multiple-dose pharmacokinetic parameters (Cmax,

Tmax,

AUC(TAU), and Ctrough) will be derived from plasma concentration versus time

for ATV, RTV

and VOR and the combined use of these drugs.

Secondary outcome

• Safety Outcome Measures: Safety assessments will be based on medical review

of adverse event

reports and the results of vital sign measurements, ECGs, physical

examinations, and clinical

laboratory tests. The incidence of observed adverse events will be tabulated

and reviewed for

potential significance and clinical importance.

Study description

Background summary

Infections with fungi and yeast frequently occur in patients infected with the human immu-nodeciency virus type 1 (HIV-1). Oropharyngeal candidiasis (OPC) and candida esophagitis (CE) have been reported to occur in up to 90% of the subjects infected with HIV and these are therefore the most common encountered opportunistic infections in these patients. As a result of highly active antiretroviral therapy (HAART), the incidence and prevalence of most opportunistic infections has decreased. OPC remains however the most frequent HIV-associated oral disease in resource limited settings or in non-compliant patients.
The occurrence of OPC and CE is associated with low CD4 T-lymphocyte counts, high viral loads and disease progression, but at the same time OPC tends to be one of the earliest opportunistic infections seen in patients with CD4 T-lymphocyte counts > 200 cells/mm3. As HIV infection progresses with declining CD4+ cells and increasing HIV viral loads, the se-verity of OPC increases with more frequent relapses, for which systemic therapy may be nec-essary.

Azole antifungal drugs are first line therapy in the treatment of oropharyngeal candidiasis and invasive fungal infections. Fluconazole is first line therapy to treat fungal infections in HIV positive patients with oral candidiasis. However, with the emergence of resistant strains, fluconazole might not provide adequate protection in all patients. Voriconazole is a second generation triazole with antifungal activity against a broad range of yeast and moulds that has been proven to be a valid alternative for fluconazole.
The combination of antiretroviral drugs (either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs)) with azole antifungal drugs is not without risk. NNRTIs may reduce the efficacy of many azole antifungals due to induction of hepatic me-tabolism. PIs themselves are influenced to a large extent when combined with potent inhibitors of enzymatic pathways (such as the azoles) leading to increased exposure to the PI with possible increased toxicity.

Atazanavir is a substrate as well as a potent inhibitor of CYP3A4. Ritonavir potently inhibits CYP3A4 and is used at low dose (100 mg QD) with ATV as a pharmacoenhancer. Ritonavir also induces multiple phase I and II enzymes including
CYP1A2, CYP2C9, CYP2C19, as well as glucuonosyl transferase.4 Voriconazole is extensively metabolized in the liver, primarily by CYP2C19 and to a lesser extent by CYP2C9 as well as CYP3A4. Voriconazole is also an inhibitor of the 3 enzymes. Given the metabolic properties of these compounds, drug - drug interactions via enzyme inhibition /induction are expected upon co-administration.
Collectively, based on the metabolic properties of ATV, RTV and VOR, the net effect of ATV/RTV on VOR exposures should not deviate significantly from the reported range after VOR and RTV 100 mg BID; VOR is unlikely to affect ATV

concentrations when dosed with ATV/RTV.
The current study is designed to test this hypothesis. When there is an indication for antifungal therapy in an HIV-infected patient, combined use of voriconazole and atazanavir / ritonavir would be an attractive option for treatment of HIV and fungal infection.

Study objective

Primary Objectives:
• To assess the effects of VOR 200 mg BID on the steady-state PK of ATV administered as ATV/RTV
300/100 mg QD in healthy subjects
• To assess the effects of ATV/RTV 300/100 mg QD on the steady-state PK of VOR 200 mg BID in
healthy subjects.

Secondary Objective(s):
• To assess the effects of VOR 200 mg BID on the steady-state PK of RTV administered as ATV/RTV
300/100 mg QD in healthy subjects
• To assess the safety and tolerability of coadministration of ATV/RTV 300/100 mg QD and VOR 200
mg BID in healthy subjects.

Study design

This is an open-label, 3-period, single-sequence, multiple dose study in healthy subjects.

Intervention

During this study, which lasts 31 days in total, subjects have to take study medication during three treatment-periods which last from 3, 10 and 10 days each.
There will be 24 participants
There is a wash-out periods of 7 days between the first and second treatment period.

Study burden and risks

Both voriconazole and atazanavir / ritonavir are well tolerated.
Participants are monitered frequently for adverse events.
Intake of medication is for a limited time period only. Also combined intake is for a limited period (10 days).
On the day of dosing an indwelling Venflon I.V. cannula will be inserted in a peripheral vein of each subject by a physician or an authorised nurse to

facilitate repeated blood sampling. The use of these needles might cause some degree of dyscomfort. The risk for the patient is very limited.

For specific, drug related, side effects, we refer to the study protocol.

Contacts

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Signed Written Informed Consent
a) The signed informed consent form.
2) Target Population
a) Healthy subjects as determined by no clinically significant deviation from normal in medical history, physical examination, ECGs, and clinical laboratory determinations.

b) Body Mass Index (BMI) of 18 to 32 kg/m2, inclusive. BMI = weight (kg)/ [height (m)]2.
3) Age and Sex
a) Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile) and men, ages 18 to 45 inclusive.
Women are considered surgically sterile only if they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy. Post menopause is defined as:
• Amenorrhea >= 12 consecutive months without another cause or
• For women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL

Exclusion criteria

1) Sex and Reproductive Status
a) WOCBP
• WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.
b) Women who are pregnant or breastfeeding
c) Women with a positive pregnancy test on enrollment or prior to administration of investigational product.
d) Sexually active fertile men not using effective birth control if their partners are WOCBP.
2) Medical History and Concurrent Diseases
a) Proven or suspected acute hepatitis (within 12 months prior to the 1st dose)
b) Any significant acute or chronic medical illness.
c) Current or recent (within 3 months) gastrointestinal disease.
d) Any major surgery within 4 weeks prior to study drug administration.
e) Any gastrointestinal surgery that could impact upon the absorption of study drug.
f) Donation of blood or plasma to a blood bank or in a clinical study (except a screening visit) within 4 weeks prior to study drug administration.
g) Blood transfusion within 4 weeks prior to study drug administration.
h) Inability to tolerate oral medication.
i) Inability to be venipunctured and/or tolerate venous access.
j) Smoking more than 5 cigarettes per day.
k) Recent (within 6 months) drug or alcohol abuse as defined in DSM IV, Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 2).

l) Any other sound medical, psychiatric and/or social reason as determined by the investigator.
m) Consumption of alcohol within 3 days prior to the first dose of study drug.
n) Intractable diarrhea (>= 6 loose stools/day for at least 7 consecutive days) within 30 days prior to the first dose of study drug.
o) History of any hemolytic disorders (including drug-induced hemolysis).
p) History of acute or chronic pancreatitis.
q) History of hypochlorhydria or achlorhydria.
3) Physical and Laboratory Test Findings
a) Men and Women < 40 Kg
b) Homozygous CYP2C19 poor metabolizers
c) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations beyond what is consistent with the target population.
d) Positive urine screen for drugs of abuse.
e) Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or HIV viral RNA or HIV-1, -2 antibody.
f) Liver enzymes (alkaline phosphatase, AST, ALT) above the upper limit of normal at screening or prior to dosing.
g) QT interval >= 500 msec, QTcF interval >= 450 msec either at screening or prior to dosing (confirmed by repeat ECG).
h) PR interval >= 210 msec, QRS interval >= 120 msec either at screening or prior to dosing (confirmed by repeat ECG).
i) First, second- or third-degree A-V block or clinically relevant ECG abnormalities either at screening or prior to dosing.
4) Allergies and Adverse Drug Reactions
a) History of allergy to ATV, RTV, VOR and related compounds.
b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).
c) Patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
5) Prohibited Treatments and/or Therapies
a) Exposure to any investigational drug or placebo within 4 weeks prior to study drug administration.
b) Use of any prescription drugs or over-the-counter acid controllers within 4 weeks prior to study drug administration.
c) Use of any other drugs, including over-the-counter medications and herbal preparations, within 1 week prior to study drug administration.
d) Use of an oral, injectable or implantable hormonal contraceptive agent within 3 months prior to study drug administration.
e) Use of St. John*s Wort (Hypericum) within 4 weeks prior to the first dose of study drug and throughout the study.
f) Consumption of grapefruit, seville orange and grapefruit juice, seville orange - containing products within 7 days prior to the first dose of study drug and throughout the study.
6) Other Exclusion Criteria
a) Prisoners or subjects who are involuntarily incarcerated
b) Subjects who are compulsorily detained for treatment of either a psychiatric or

physical (eg, infectious disease) illness

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-01-2010
Enrollment:	24
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Norvir
Generic name:	Ritonavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Reyataz
Generic name:	Atazanavir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Vfend
Generic name:	Voriconazole
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-04-2009
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-04-2009
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-04-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-04-2011
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-009095-13-NL
CCMO	NL27011.091.09